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Health Effects Assessment for Dieldrin

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HEALTH EFFECTS ASSESSMENT
FOR DIELDRIN

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16. ABSTRACT This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_s or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q₁*s have been computed, if appropriate, based on oral and inhalation data if available.		
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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with dieldrin. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for Aldrin/Dieldrin. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-018. NTIS PB81-117301.

U.S. EPA. 1980b. Hazard Profile for Dieldrin. Prepared by the Office of Environmental Health and Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Solid Waste, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_s (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RfD_s estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980c) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_o) or inhalation (RfD_i) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity RfDs and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980c). Since cancer is a process that is not characterized by a threshold, any exposure contributes an increment of risk. For carcinogens, q₁*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

The risk assessment for dieldrin is based on positive results in several carcinogenicity bioassays. The U.S. EPA (1986) calculated a human carcinogenic potency factor (q_1^*) of $16 \text{ (mg/kg/day)}^{-1}$ based on the geometric mean of 13 animals bioassays. No additional data were found in a review of more recent literature or the CBI files, and this value is still recommended.

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LIST OF ABBREVIATIONS

CAS	Chemical Abstract Service
CBI	Confidential business information
EEG	Electroencephalogram
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
NOAEL	Lowest-observed-adverse-effect level
NOEL	No-observed-effect level
ppb	Parts per billion
ppm	Parts per million
RfD	Reference dose
RfD _I	Inhalation reference dose
RfD _O	Oral reference dose
RfD _S	Subchronic reference dose
RfD _{SI}	Subchronic inhalation reference dose
RfD _{SO}	Subchronic oral reference dose
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TLV	Threshold limit value

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected physical and chemical properties and half-lives for dieldrin are listed in Table 1-1.

Little is known about the fate of dieldrin in the atmosphere. Because of its low vapor pressure, dieldrin will probably remain associated with particulate matter in the atmosphere. Vapor phase photodegradation has been noted but its rate is unknown (HSDB, 1986).

In water, dieldrin is expected to persist in sediments and bioconcentrate in aquatic organisms. Volatilization should be an important pathway for ultimate removal of dieldrin. The estimated volatilization half-lives of unadsorbed dieldrin range from 6-9 hours to up to 72 days in ponds; however, the actual volatilization half-life will exceed these estimated values because of strong adsorption. In addition, direct photolysis of dieldrin to photodieldrin may occur (half-life of ~4 months or somewhat less in the presence of photosensitizers). In a modelling study of a reservoir, it was concluded that 40% of dieldrin in the in-flow was lost to the bottom by sedimentation; 50% was released through the out-flow because of the short detention time in the reservoir; and 10% was taken up by fish (HSDB, 1986).

In soil, dieldrin will persist for extremely long periods of time (5-25 years) (U.S. EPA, 1980a). Its low water solubility and strong adsorption to soil make leaching into most groundwater unlikely (HSDB, 1986).

TABLE 1-1

Selected Physical and Chemical Properties and Half-lives for Dieldrin

Property	Value	Reference
CAS number:	60-57-1	
Chemical class:	chlorinated pesticides	
Molecular weight:	380.93	
Vapor pressure:	1.78×10^{-7} mm Hg at 20°C	U.S. EPA, 1980a
Water solubility:	0.186 mg/l at 25-29°C	U.S. EPA, 1980a
Log octanol/water partition coefficient:	4.32, 5.48, 6.20	Kanazawa, 1981; Hawker and Connell, 1986; Hansch and Leo, 1985
Bioconcentration factor:	10^2 - 10^4 (various aquatic species) 3-6000 (fish)	HSDB, 1986
Soil adsorption coefficient:	7.41×10^3	HSDB, 1986
Half-lives:		
Water	~300 days (lakes)	Zoeteman et al., 1980
Soil	1-6 years (estimated) (estimated from 95% removal time)	U.S. EPA, 1980a

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Heath and Vandekar (1964) reported that absorption of radiolabeled dieldrin by the upper gastrointestinal tract of rats begins almost immediately following an oral dose and that absorption varies with the solvent used. Ahdaya et al. (1978) reported that gastrointestinal absorption of dieldrin was the slowest of several compounds tested, while Deichmann (1981) and Quaife and Fitzhugh (1967) reported that dieldrin was absorbed readily from the gastrointestinal tract. Ahdaya and Guthrie (1982) found that 63.2% of an oral dose of 1 mg/kg dieldrin in a 1:1:8 emulphor:ethanol:water mixture was absorbed from the gastrointestinal tract within 60 minutes. When the stomach was ligated, only 13.9% of the dose was absorbed in 60 minutes, indicating that absorption from the small intestine was the primary route of dieldrin uptake; however, Tanaka et al. (1981) reported that dieldrin was absorbed slowly from the small intestine.

2.2. INHALATION

Deichmann (1981) reported that dieldrin was readily absorbed from the respiratory tract.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Hunter et al. (1969) administered HEOD, the pure compound in a formulation of dieldrin, to human subjects at doses of 10, 50 or 211 µg/day for 2 years. Although the focus of the study was pharmacodynamics, several clinical parameters reflecting health of the subject were monitored. No adverse effects on health of the subjects occurred at any dose level.

There are several subchronic studies available in which dieldrin was administered orally to laboratory animals. Bandyopadhyay et al. (1982) administered 0 or 5 mg/kg/day dieldrin by gavage in corn oil to rats for 15 days and found histopathological changes in the liver and kidneys of rats given dieldrin. Den Tonkelaar and Van Esch (1974) conducted 2-week studies with groups of 3-6 male rats receiving 0, 2, 5, 10, 20 or 50 ppm dieldrin in the diet, and examined effects on hepatic microsomal enzymes. They determined that 5 ppm was a LOEL and 2 ppm a NOEL for induction of these enzymes. Shakoori et al. (1984) fed dieldrin in the diet to male rats at a dosage of 2 mg/kg/day for 6 months, and found that several serum biochemical parameters, including SGOT and SGPT activities, were significantly increased in the treated rats after the 6-month exposure. Walker et al. (1969) administered dieldrin (>99% purity) in gelatin capsules to groups of five male and five female beagle dogs at dosages of 0, 0.005 and 0.05 mg/kg/day for 2 years. Treated dogs were healthy, as indicated by body weights, EEG tracings, urinalysis, and hematological and clinical chemistry evaluations. The high-dose dogs had significantly increased liver weights relative to controls, but no tissue lesions were found. Fitzhugh et al. (1964) treated 14 mongrel dogs with dieldrin in the diet at dosages of 0.2-10 mg/kg/day, 6

days/week for up to 25 months. Gross toxic effects (weight loss, convulsions) and histopathological changes including fatty degeneration of liver and kidneys and reduced cellularity of the bone marrow occurred at ≥ 0.5 mg/kg/day.

Smith (1973) and Van Gelder and Smith (1973) conducted subchronic behavioral experiments with squirrel monkeys receiving dieldrin at oral doses of 0.1 or 0.01 mg/kg/day for 55 days. The higher dosage impaired learning behavior, but the lower dosage had no effect.

3.1.2. Inhalation. Subchronic inhalation studies with dieldrin could not be located in the available literature.

3.2. CHRONIC

3.2.1. Oral. In a study of occupational exposure to dieldrin, Van Raalte (1977) found that intoxication occurred at blood levels of 280-290 ppb, while 200 ppb (corresponding to a daily oral intake of 2 mg/person/day) was a NOEL.

Fitzhugh et al. (1964) fed groups of 12 male and 12 female Osborne-Mendel rats diets containing 0, 0.5, 2, 10, 50, 100 or 150 ppm dieldrin for 2 years. Growth was unaffected, but survival was reduced in a dose-related manner at concentrations of ≥ 50 ppm. All treated rats had increased relative liver weights and dose-related histopathological liver lesions. Rats at the higher doses had distended and hemorrhagic urinary bladders and an increased incidence of nephritis.

Hodge et al. (1967) reviewed a large number of subchronic and chronic studies, and attempted to define thresholds for a variety of toxic effects in different species. The lowest dietary concentration found to cause adverse effects was 0.5 ppm, which resulted in increased relative liver weight and histopathological liver effects in female rats fed this diet for

2 years. Hodge et al. (1967) concluded that no NOEL had yet been determined for these effects, which were the most sensitive indicators of dieldrin toxicity. Dogs fed 1 ppm dieldrin in the diet for 15 months had increased relative liver weights. Histopathological effects in liver occurred in dogs at 8 ppm in the diet for 10 months but not at 3 ppm for 15 months. Mice fed 10 ppm dieldrin in the diet for 2 years also experienced histopathological effects in the liver.

Wright et al. (1978) conducted long-term (~6 years) studies with groups of five male rhesus monkeys receiving diets containing dieldrin at concentrations of 0.01-5.00 ppm. The only observed treatment-related histological effects were "small changes associated with the hepatocellular endoplasmic reticulum." The most sensitive effects were changes in hepatic microsomal monooxygenases, which occurred at dietary concentrations of 1.75 and 5 ppm. The threshold for the induction of these enzymes was 25-30 µg/kg/day, which corresponded to a liver concentration of 6-7 ppm. In rats and mice, liver dieldrin concentrations of this magnitude are associated with substantial enzyme induction and liver enlargement. The results of this study and the absence of detectable liver changes in humans with high endogenous dieldrin concentrations indicate that the livers of primate species may be relatively insensitive to dieldrin-induced effects (Wright et al., 1978).

Reuber (1980) reported results of a chronic toxicity study in which groups of 12 male and 12 female Osborne-Mendel rats were fed diets containing 0.5, 2, 10, 50, 100 or 150 ppm dieldrin for 2 years. The incidence and severity of chronic nephritis was increased in rats exposed to ≥ 50 ppm. Many animals in the 100 and 150 ppm groups died from renal necrosis or hepatic necrosis. High mortality of rats at ≥ 50 ppm prevented detection of late-developing tumors in those groups.

Harr et al. (1970a) conducted a factorial experiment in which groups of OSU-Wistar rats were exposed to dietary dieldrin. The two factors investigated were dietary concentrations of dieldrin (0.08-40.0 ppm) and age of the rats (28-750 days). Dieldrin treatment resulted in nonspecific neural and vascular lesions, cranial edema and convulsions. No functional effects on the neural or vascular system occurred at concentration <2.1 ppm.

3.2.2. Inhalation. Chronic inhalation studies with dieldrin could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Chernoff et al. (1975) and Dix et al. (1977) obtained negative results in teratogenicity studies using mice and rats. Chernoff et al. (1975) administered 0, 1.5, 3.0 or 6.0 mg/kg/day dieldrin by gavage in peanut oil to groups of 9-25 pregnant CD rats and groups of 6-16 pregnant CD-1 mice on days 7-16 of gestation. The highest dose caused 41% mortality in rats and increased relative liver weight and decreased body weight gain in mice. No teratogenic effects were observed. The two highest doses were associated with an increased percentage of supernumerary ribs in mice. Dix et al. (1977) administered 0, 1.5 or 4.0 mg/kg/day HEOD (purified dieldrin) in corn oil to pregnant CF1 mice by gavage on days 6-14 of gestation. No compound-related maternal toxicity, fetotoxicity or teratogenic effects were observed.

Several studies have addressed possible reproductive effects of dieldrin in rats and mice. Agarwal and Ahmad (1979) reported that 12.5 ppm dieldrin in the diet caused reduced fertility and high pup mortality in rats and mice. No other details were provided. Good and Ware (1969) found that feeding a diet containing 5 ppm dieldrin to CFW Swiss mice for 120 days beginning 30 days before mating resulted in reduced litter size. No effects

on fertility or fecundity were noted. Keplinger et al. (1968) reported that a dietary level of 25 ppm dieldrin caused "marked" effects on fertility, gestation, viability, lactation or survival of mice in a multigeneration study. Significant but less severe effects occurred at 3 and 10 ppm dieldrin. No other details were provided. Harr et al. (1970b) conducted an experiment in which groups of OSU-Wistar rats were exposed to dietary dieldrin concentrations of 0.08-40.0 ppm for 39-750 days. The higher concentrations caused mortality. Dieldrin exposure decreased the percentage of females that conceived and therefore the number of nursing pups. The calculated maximum dietary concentration that did not cause any reproductive effects (conception rate, pup survival, litter size) was 0.24 ppm, a level that was equivalent to 0.014 mg/kg/day according to the authors.

In a review of several unpublished studies, Hodge et al. (1967) reported that the lowest dietary dieldrin concentration that caused reproductive effects was 2.5 ppm, which caused increased pup mortality and fewer pregnancies in rats. This was the lowest concentration tested in any of the available studies at that time, and therefore, a NOAEL could not be determined. This concentration was higher than the LOAEL (0.5 ppm) reported for increased relative liver weights and histopathological changes in the liver in rats (Hodge et al., 1967). Dogs were somewhat less sensitive, with increased pup mortality at 25 ppm but not 8 ppm (Hodge et al., 1967).

Clegg (1979) reviewed studies concerning the reproductive effects of pesticides. In one of these studies, rats fed 0.1 or 1 ppm dieldrin in the diet were unaffected, but 2 ppm caused reduced survival to weaning in the F_{1a} generation. In another study, 60 ppm dieldrin in the diet of rats caused decreased mating success. A multigeneration mouse study showed that

10 and 25 ppm dieldrin in the diet caused reduced survival and viability of pups. Only "non-consistent reduction of lactation index" was reported at 3 ppm, the lowest dose tested.

3.3.2. Inhalation. Pertinent studies concerning teratogenicity or reproductive effects of inhaled dieldrin could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

Several studies are available concerning effects of dieldrin administered in combination with other pesticides. Ehrich et al. (1976) found that an oral dose of 16 mg/kg dieldrin had no effect on the anticholinesterase action of dichlorvos. Deichmann et al. (1969) reported results of several studies that showed that dieldrin storage in adipose tissue of rats and dogs was reduced when DDT was administered concurrently. Menzer (1970) fed dieldrin to mice at a dietary concentration of 5 or 25 ppm for 7 or 14 days, and then administered various organophosphate pesticides by intraperitoneal injection. Dieldrin pretreatment decreased the toxicity of Bidrin® and phosphamidon, slightly decreased the toxicity of malathion and increased the toxicity of dimethoate. Thomas et al. (1974) reported that simultaneous administration of dieldrin and parathion had similar effects on androgen metabolism and hepatic microsomal enzymes as dieldrin alone. Jones et al. (1974) found that addition of 100 ppm dieldrin to a diet containing 900 ppm hexachlorophene reduced mortality of rats fed hexachlorophene alone for 8 weeks from 100% to <4%. The authors speculated that the modification of hexachlorophene toxicity by dieldrin may have been due to enzyme induction.

Another study reported effects of chemicals other than pesticides on dieldrin toxicity. Uzoukwu and Sleight (1972) found that sodium nitrite did not potentiate dieldrin toxicity in guinea pigs.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Human oral carcinogenicity studies could not be located in the available literature.

4.1.2. Inhalation. Jager (1970) and Versteeg and Jager (1973) reported results of studies of 233 pesticide workers exposed to aldrin, dieldrin, endrin and telodrin for 4-13 years in Holland. No adverse health effects, including cancer, attributable to pesticide exposure were detected. Van Raalte (1977) conducted a follow-up study, presumably of the same group of workers, and found no adverse health signs and no increase in cancer incidence. The author suggested that these results indicated that dieldrin is not a human carcinogen. In reviewing this study, however, U.S. EPA (1980a) noted that the total number of subjects in this study was small and that the observation times may have been too short (i.e., <20 years).

4.2. BIOASSAYS

4.2.1. Oral. U.S. EPA (1980a) reviewed and evaluated several studies of the carcinogenicity of dieldrin (Table 4-1). U.S. EPA (1986b) reviewed the studies shown in Table 4-2. Mice appeared to be the species most sensitive to dieldrin carcinogenicity; the liver was the principal organ affected. Results from rat studies were generally negative. Of the studies discussed by U.S. EPA (1986b), the Thorpe and Walker (1973) bioassay in mice was determined to be the most useful for risk assessment.

In the Thorpe and Walker (1973) study, diets containing 10 ppm dieldrin (>99% pure) were fed to groups of 30 CF₁ mice of both sexes for 110 weeks. The control group consisted of 45 mice of both sexes. The mice were bred and maintained in individual cages under specific-pathogen-free conditions. Treatment commenced at 4 weeks of age; all survivors were sacrificed after the 110-week exposure. Moribund animals were sacrificed

TABLE 4-1
Summary of Carcinogenicity Data for Dieldrin

Strain/ Species	Number/Sex/Group	Dose/Exposure	Length of Study	Compound Purity	Effects	Reference
F344 rats	21/sex/group	0, 2, 10, 50 ppm diet for 104-105 weeks	104-105 weeks	technical	Signs of organochlorine intoxication (tremors, hyperexcitability) in high- dose rats of both sexes; no compound- related increased incidence of neoplasms	MCL, 1977b
Osborne- Mendel rats	50/sex/group	29 ppm diet for 80 weeks or 65 ppm diet for 59 weeks	110-111 weeks	technical	Significantly increased combined inci- dence of adrenal cortical adenoma or carcinoma in females (6/45) relative to pooled controls (0/55), but not in high- dose females (2/40); not significant when compared with matched controls	MCL, 1977a
Osborne- Mendel rats	12/sex/group	0, 0.5, 2, 10, 50, 100, 150 ppm diet for 2 years	2 years	100%	Reduced survival at ≥ 50 ppm and no in- crease in liver tumors; high incidence of multiple-site tumors at lower concentra- tions; dose-related liver lesions and increased relative liver weights at all doses; histopathological effects on kidneys and urinary bladder at higher doses	Fitzhugh et al., 1964
Carworth rats	25/sex/group (45/sex/control group)	0, 0.1, 1, 10 ppm diet for 2 years	2 years	99%	High mortality in all groups; no signifi- cant treatment-related effects on tumor incidence	Walker et al., 1969
Osborne- Mendel rats	50/sex/group (100/sex for control group)	0, 20, 30, 50 ppm diet for 2 years	2 years	technical	No treatment-related increase in liver tumors; decrease in total tumors in treated rats	Beichmann et al., 1970
Carworth rats		0, 2.5, 12.5, 25 ppm diet for 2 years	2 years		No treatment-related increase in any type of tumor; increased mortality and relative liver weights in treated rats at all doses	Treon and Cleveland, 1955
B6C3F1 mice	50/sex/treated group; 20 males, 10 females in matched control groups; 92 males, 79 females in pooled control groups	0, 2.5, 5 ppm diet for 80 weeks	90-93 weeks	technical	Significant positive dose-related trend in hepatocellular carcinomas in male mice (pooled controls, 17/92; low dose, 12/50, high dose, 16/45)	MCL, 1977a

TABLE 4-1 (cont.)

Strain/ Species	Number/Sex/Group	Dose/Exposure	Length of Study	Compound Purity	Effects	Reference
Cf1 mice	300/sex/group 125/sex/group 125/sex/group 200/sex/group	0 ppm 0.1 ppm 1.0 ppm 10.0 ppm diet for 132 weeks	132 weeks	99.5%	Accelerated mortality rate at 10.0 ppm; dose-related increase in liver tumors, both sexes; males-control 20%, low dose 26%, mid-dose 31%, high dose 94%; females-control 12%, low dose 27%, mid-dose 37%, high dose 92%	Walker et al., 1972
Cf1 mice	30/sex/group (78/sex/control group)	0, 1.25, 2.5, 5, 10 or 20 ppm diet for 128 weeks	128 weeks	99.5%	Mortality of mice in the two highest dose groups resulted in too few animals for comparison, liver tumor incidence was dose-related in the other groups: males-control 12%, 1.25 ppm 20%, 2.5 ppm 43%, 5 ppm 87%; females-control 10%, 1.25 ppm 17%, 2.5 ppm 43%, 5 ppm 60%	Walker et al., 1972
Cf1 mice	30/sex/group (45/sex for control group)	0, 10 ppm diet for 100 weeks	100 weeks	99.5%	High incidence of liver tumors in treated mice - 100% males and 87% females at the end of the study	Thorpe and Walker, 1973
C3H mice	215-218/group, approximately equally divided by sex	0, 10 ppm diet for 2 years	2 years	NR	Significant increase in hepatomas in treated mice; high mortality in all groups; shorter lifespan in treated mice	Davis and Fitzhugh, 1962
C3H mice	100/HR/group	0, 10 ppm diet for 2 years	2 years	NR	Reduced survival in treated mice; increase in benign hyperplasia and benign hepatomas in treated mice	Davis, 1965
Syrian golden hamsters	32-41/group both sexes	0, 20, 60, 80 ppm diet for 120 weeks	120 weeks	99%	Increased number of animals with multiple tumors and increase in incidence of adrenal tumors in treated hamsters, but neither was statistically significant	Cabot et al., 1979
Beagle dogs	5/sex/group	0, 0.005, 0.05 mg/kg/day, in gelatin capsules for 2 years	2 years	99.5%	Increased relative liver weight in high-dose dogs; no treatment-related lesions or tumors	Walker et al., 1969
Mongrel dogs	26/HR	0.2-10.0 mg/kg/ day, 6 days/week for up to 25 months	25 months	99%	Gross toxic effects (weight loss, convulsions), microscopic changes in liver, kidney and bone marrow at >0.5 mg/kg/day; no effects at 0.2 mg/kg/day; no treatment-related tumors were reported	Fitzhugh et al., 1964

NR - Not reported

TABLE 4-2

Summary of Pertinent Cancer Studies on Mice Using Dieldrin
Reviewed By U.S. EPA (1986b)

Sex, Strain	Tumor Site and Type	Potency (mg/kg/day) ⁻¹	Potency Index (mmol/kg/day) ⁻¹	Reference
Female, CF ₁	liver, carcinoma	28.60	1.1x10 ⁴	Walker et al., 1972
Female, CF ₁	liver, carcinoma	25.00	9.5x10 ³	Davis and Fitzhugh, 1962,
Male, CF ₁	liver, carcinoma	24.81	9.5x10 ³	Walker et al., 1972
Male, CF ₁	liver, carcinoma	22.02	8.4x10 ³	Davis and Fitzhugh, 1962,
Male, B6C3F ₁	liver, carcinoma	9.13	3.5x10 ³	NCI, 1978a

during the study; all animals were grossly examined. The sections of brain, heart, lungs, liver, kidneys, and testes or ovaries, and all macroscopic lesions were processed and microscopically examined. In the mice fed dieldrin, liver enlargement was detected after 50 weeks in both sexes with mortality increased after 22 months. Liver lesions were arbitrarily classified as Type A or Type B.

Dieldrin induced a statistically significant increase ($p < 0.01$) in the incidence of liver tumors in both sexes as compared with controls. Metastases were found only in the lungs of animals with Type B tumors. As in a previous study by Walker et al. (1972), Type B tumors were not detected in female controls and were present in only a small proportion (4% of male controls).

In contrast to the earlier study of Walker et al. (1972), tumor incidences versus time were presented. Liver tumors appeared much earlier in the treated animals than in controls in that 50 and 100% of all dieldrin-treated females and males, respectively, that died by 17 months had liver tumors; no liver tumors, however, were found in controls at that time.

In the NCI (1977a) studies, groups of 50 male and 50 female B6C3F1 mice were fed diets containing 2.5 or 5 ppm technical grade dieldrin for 80 weeks, followed by a 10- to 13-week observation period before sacrifice. Matched control groups consisted of 20 untreated males and 10 untreated females. Pooled controls consisted of the matched controls plus untreated mice from bioassays with other chemicals (92 males and 79 females). There was a significant positive dose-related trend in the incidence of hepatocellular carcinomas in male mice when pooled controls were used for comparison. Incidences were 17/92 for pooled controls, 12/50 for low-dose mice and 16/45 for high-dose mice.

In the Walker et al. (1972) study, groups of 300, 125, 125 and 200 CF1 mice of each sex were fed diets containing 0, 0.1, 1.0 or 10.0 ppm dieldrin (99+% purity), respectively, for 132 weeks. There was a dose-related increase in individual and combined incidences of benign and malignant liver tumors in both sexes. In males, combined liver tumor incidences were reported as 20% for controls, 26% for low-dose, 31% for middle-dose and 94% for high-dose mice. In females, combined liver tumor incidences were reported as 13% for controls, 27% for low-dose, 37% for middle-dose and 92% for high-dose mice. Survival of high-dose mice was reduced relative to controls.

4.2.2. Inhalation. Inhalation studies of the carcinogenicity of dieldrin could not be located in the available literature.

4.3. OTHER RELEVANT INFORMATION

Dieldrin has given negative results in mutagenicity assays with micro-organisms, including Salmonella typhimurium with or without metabolic activation (U.S. EPA, 1980a; Ashwood-Smith, 1981). Ashwood-Smith (1981) reported that mutagenicity findings in several mammalian studies were equivocal because of a lack of positive controls or a dose-response relationship or both. Bidwell et al. (1975) and Dean et al. (1975) reported that dieldrin gave negative results in several mammalian mutagenicity assays.

4.4. WEIGHT OF EVIDENCE

IARC (1982) classified dieldrin as a Group 3 compound, i.e., a compound that could not be classified according to its carcinogenicity. This classification probably reflects categorizing the evidence for carcinogenicity in animals as "limited," based on the observation that the only tumor type consistently associated with treatment was liver tumors in mice, which are

known to have a high background incidence. According to the U.S. EPA classification scheme (U.S. EPA, 1986a), dieldrin belongs in Group B2, i.e., Probable Human Carcinogen, which reflects sufficient evidence for carcinogenicity to animals there being multiple studies with liver tumor responses in mice which withstand the downgrading provisions of the U.S. EPA cancer guidelines. Also, some evidence of carcinogenic activity is seen in a second species, the rat (U.S. EPA, 1986b).

5. REGULATORY STANDARDS AND CRITERIA

The U.S. EPA (1980a) derived cancer-based ambient water quality criteria for dieldrin using data from the Walker et al. (1972) mouse study. The recommended criteria corresponding to an incremental increase in excess lifetime cancer risk of 10^{-5} , 10^{-6} and 10^{-7} were 0.71, 0.071 and 0.0071 ng, respectively. These estimates were made to protect against dieldrin exposure through ingestion of contaminated water and aquatic organisms. Estimates made for the consumption of aquatic organisms only are 0.76, 0.076 and 0.0076 ng/l, respectively.

Vettorazi (1975) reported an FAO/WHO ADI of 0.0001 mg/kg/day for aldrin plus dieldrin. ACGIH (1986) and OSHA (1983) have recommended 0.25 mg/m³ as a criterion for dieldrin in the atmosphere. In recommending this TLV, ACGIH (1986) noted that the TLV was believed to be sufficiently low to prevent systemic toxicity.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

Because dieldrin is classified as a carcinogen, no RfD_{SO} or RfD_{SI} will be derived.

6.2. REFERENCE DOSE (RfD)

Because dieldrin is classified as a carcinogen, no RfD_0 or RfD_I will be derived.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. Thirteen data sets are suitable for quantitative risk estimation. The most sensitive sex and strain tested is male CF_1 mice in the Thorpe and Walker (1973) study shown in Table 6-1. From these data (Tables 6-1 through 6-13) the potency can be estimated at 55 per mg/kg/day.

The most sensitive species tested is mice. There are 13 potency estimates, ranging from 55 down to 7 per mg/kg/day, with a geometric mean of 16 per mg/kg/day. Therefore the potency for the general population or human q_1^* is estimated at 16 per mg/kg/day.

These estimates are plausible upper bounds for the increased cancer risk from dieldrin, meaning that the true risk is not likely to exceed these estimates and may be lower. This estimate of oral carcinogenic potency is adopted for the purposes of this document.

Review of the CBI file for dieldrin did not reveal any information that would modify this assessment.

6.3.2. Inhalation. Data are insufficient to calculate an inhalation q_1^* for dieldrin.

TABLE 6-1

Cancer Data Sheet for Derivation of Potency of Dieldrin
from Tumor Incidence in Mice†

Compound: dieldrin
Species, Strain, Sex: mouse, CF₁, male
Body Weight: 0.030 kg (assumed)
Length of Experiment: 110 weeks
Length of Exposure: 110 weeks
Tumor Site and Type: liver
Route, Vehicle: oral, diet
Human Potency (q1*): 55 per mg/kg/day

Experimental Dose (ppm)	Average Daily Dose (mg/kg/day)	Human Equivalent Dose (mg/kg/day)*	Tumor Incidence*
0	0.00	0.000	11/45
10	1.30	0.098	30/30

†Source: Thorpe and Walker, 1973

*Note: To calculate human potency, a tumor incidence of 29/30 was used and the dose was adjusted to 29/30 of the above value.

TABLE 6-2

Cancer Data Sheet for Derivation of Potency of Dieldrin
from Tumor Incidence in Mice†

Compound: dieldrin
Species, Strain, Sex: mouse, CF₁, female
Body Weight: 0.030 kg (assumed)
Length of Experiment: 110 weeks
Length of Exposure: 110 weeks
Tumor Site and Type: liver
Route, Vehicle: oral, diet
Human Potency (q1*): 26 per mg/kg/day

Experimental Dose (ppm)	Average Daily Dose (mg/kg/day)	Human Equivalent Dose (mg/kg/day)	Tumor Incidence
0	0.00	0.000	10/44
10	1.30	0.104	26/30

†Source: Thorpe and Walker, 1973

TABLE 6-3

Cancer Data Sheet for Derivation of Potency of Dieldrin
from Tumor Incidence in Mice†

Compound: technical-grade dieldrin
 Species, Strain, Sex: mice, B6C3F₁, male
 Body Weight: 0.030 kg (assumed)
 Length of Experiment: 93 weeks
 Length of Exposure: 80 weeks
 Tumor Site and Type: liver, carcinoma
 Route, Vehicle: oral, diet
 Human Potency (q1*): 9.8 per mg/kg/day

Experimental Dose (ppm)	Transformed Dose (mg/kg/day)	Human Equivalent Dose (mg/kg/day)*	<u>Incidence</u> No. Responding/ No. Examined
0	0	0	17/92
2.5	0.325	0.026	12/50
5	0.65	0.052	16/45

†Source: Thorpe and Walker, 1977a

*Note: Human equivalent doses were multiplied by 80/93 to reflect exposure less than the duration of the experiment.

TABLE 6-4

Cancer Data Sheet for Derivation of Potency of Dieldrin
from Tumor Incidence in Mice†

Compound: dieldrin
Species, Strain, Sex: mice, C3H, male
Body Weight: 0.030 kg (assumed)
Length of Experiment: 2 years
Length of Exposure: 2 years
Tumor Site and Type: liver, carcinoma
Route, Vehicle: oral, diet
Human Potency (q1*): 22 per mg/kg/day

Experimental Dose (ppm)	Transformed Dose (mg/kg/day)	Human Equivalent Dose (mg/kg/day)	<u>Incidence</u>
			No. Responding/ No. Examined
0	0	0	22/73
10	1.3	0.104	62/71

†Source: Davis, 1965

TABLE 6-5

Cancer Data Sheet for Derivation of Potency of Dieldrin
from Tumor Incidence in Mice†

Compound: dieldrin
Species, Strain, Sex: mice, C3H, female
Body Weight: 0.030 kg (assumed)
Length of Experiment: 2 years
Length of Exposure: 2 years
Tumor Site and Type: liver, carcinoma
Route, Vehicle: oral, diet
Human Potency (q1*): 25 per mg/kg/day

Experimental Dose (ppm)	Transformed Dose (mg/kg/day)	Human Equivalent Dose (mg/kg/day)	<u>Incidence</u> No. Responding/ No. Examined
0 10	0 1.3	0 0.104	2/53 62/71

†Source: Davis, 1965

TABLE 6-6

Cancer Data Sheet for Derivation of Potency of Dieldrin
from Tumor Incidence in Mice†

Compound: dieldrin
Species, Strain, Sex: mice, CF₁, male
Body Weight: 0.030 kg (assumed)
Length of Experiment: 33 months
Length of Exposure: 24 months
Tumor Site and Type: liver, carcinoma
Route, Vehicle: oral, diet
Human Potency (q1*): 25 per mg/kg/day

Experimental Dose (ppm)	Transformed Dose (mg/kg/day)	Human Equivalent Dose (mg/kg/day)	<u>Incidence</u> No. Responding/ No. Examined
0	0	0	58/288
0.1	0.013	0.001	32/124
1.0	0.13	0.01	34/111
10.0	1.3	0.104	165/176

†Source: Walker et al., 1972

TABLE 6-7

Cancer Data Sheet for Derivation of Potency of Dieldrin
from Tumor Incidence in Mice†

Compound: dieldrin
Species, Strain, Sex: mice, CF₁, male
Body Weight: 0.030 kg (assumed)
Length of Experiment: 33 months
Length of Exposure: 24 months
Tumor Site and Type: liver, carcinoma
Route, Vehicle: oral, diet
Human Potency (q1*): 28 per mg/kg/day

Experimental Dose (ppm)	Transformed Dose (mg/kg/day)	Human Equivalent Dose (mg/kg/day)	<u>Incidence</u>
			No. Responding/ No. Examined
0	0.0013	0.0001	39/297
0.1	0.013	0.001	24/90
1.0	0.13	0.01	32/87
10.0	1.3	0.104	136/148

†Source: Walker et al., 1972

TABLE 6-8

Cancer Data Sheet for Derivation of Potency of Dieldrin
from Tumor Incidence in Mice†

Compound: dieldrin
Species, Strain, Sex: mouse, CF₁, male
Body Weight: 0.030 kg (assumed)
Length of Experiment: 128 weeks
Length of Exposure: 128 weeks
Tumor Site and Type: liver
Route, Vehicle: oral, diet
Human Potency (q1*): 15 per mg/kg/day

Experimental Dose (ppm)	Average Daily Dose (mg/kg/day)	Human Equivalent Dose (mg/kg/day)	Tumor Incidence
0	0.00	0.000	9/78
1.25	0.16	0.012	6/30
2.5	0.33	0.025	13/30
5	0.65	0.049	26/30
10	1.30	0.098	5/11
20	2.60	0.196	12/17

†Source: Walker et al., 1972

TABLE 6-9

Cancer Data Sheet for Derivation of Potency of Dieldrin
from Tumor Incidence in Mice†

Compound: dieldrin
Species, Strain, Sex: mouse, CF₁, female
Body Weight: 0.030 kg (assumed)
Length of Experiment: 128 weeks
Length of Exposure: 128 weeks
Tumor Site and Type: liver
Route, Vehicle: oral, diet
Human Potency (q1*): 7.1 per mg/kg/day

Experimental Dose (ppm)	Average Daily Dose (mg/kg/day)	Human Equivalent Dose (mg/kg/day)	Tumor Incidence
0	0.00	0.000	8/78
1.25	0.16	0.012	5/30
2.5	0.33	0.025	12/28
5	0.65	0.049	18/30
10	1.30	0.098	9/17
20	2.60	0.196	8/21

†Source: Walker et al., 1972

TABLE 6-10

Cancer Data Sheet for Derivation of Potency of Dieldrin
from Tumor Incidence in Mice†

Compound: dieldrin
Species, Strain, Sex: mouse, CF₁, male
Body Weight: 0.030 kg (assumed)
Length of Experiment: 110 weeks
Length of Exposure: 110 weeks
Tumor Site and Type: liver
Route, Vehicle: oral, diet
Human Potency (q1*): 18 per mg/kg/day

Experimental Dose (ppm)	Average Daily Dose (mg/kg/day)	Human Equivalent Dose (mg/kg/day)	Tumor Incidence
0	0.00	0.000	25/252
10	1.30	0.104	113/139

†Source: Tennekes et al., 1981

TABLE 6-11

Cancer Data Sheet for Derivation of Potency of Dieldrin
from Tumor Incidence in Mice†

Compound: dieldrin
Species, Strain, Sex: mouse, C57BL/6J, male
Body Weight: 0.030 kg (assumed)
Length of Experiment: 132 weeks
Length of Exposure: 85 weeks
Tumor Site and Type: liver, hepatocellular carcinoma
Route, Vehicle: oral, diet
Human Potency (q1*): 7.4 per mg/kg/day

Experimental Dose (ppm)	Average Daily Dose (mg/kg/day)	Human Equivalent Dose (mg/kg/day)*	Tumor Incidence
0	0.00	0.000	0/69
10	1.30	0.104	21/71

†Source: Meierhenry et al., 1983

*Note: Human Equivalent doses were multiplied by 85/132, to reflect exposure less than the duration of the experiment.

TABLE 6-12

Cancer Data Sheet for Derivation of Potency of Dieldrin
from Tumor Incidence in Mice†

Compound: dieldrin
Species, Strain, Sex: mouse, C3H/He, male
Body Weight: 0.030 kg (assumed)
Length of Experiment: 132 weeks
Length of Exposure: 85 weeks
Tumor Site and Type: liver, hepatocellular carcinoma
Route, Vehicle: oral, diet
Human Potency (q1*): 8.5 per mg/kg/day

Experimental Dose (ppm)	Average Daily Dose (mg/kg/day)	Human Equivalent Dose (mg/kg/day)*	Tumor Incidence
0	0.00	0.000	6/50
10	1.30	0.104	19/50

†Source: Meierhenry et al., 1983

*Note: Human Equivalent doses were multiplied by 85/132, to reflect exposure less than the duration of the experiment.

TABLE 6-13

Cancer Data Sheet for Derivation of Potency of Dieldrin
from Tumor Incidence in Mice†

Compound: dieldrin
Species, Strain, Sex: mouse, B6C3F₁, male
Body Weight: 0.030 kg (assumed)
Length of Experiment: 132 weeks
Length of Exposure: 85 weeks
Tumor Site and Type: liver, hepatocellular carcinoma
Route, Vehicle: oral, diet
Human Potency (q1*): 11 per mg/kg/day

Experimental Dose (ppm)	Average Daily Dose (mg/kg/day)	Human Equivalent Dose (mg/kg/day)*	Tumor Incidence
0	0.00	0.000	3/76
10	1.30	0.104	26/62

†Source: Melerhenry et al., 1983

*Note: Human Equivalent doses were multiplied by 85/132, to reflect exposure less than the duration of the experiment.

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